Claim amendments

Claims 1 and 4 and 7 have been amended and claim 5 incorporated into claim 1 to overcome 35 U.S.C. 112, first paragraph, and 35 U.S.C. 103(a) rejections over **Adams** *et al.* and **Hartman** *et al.* and **Simonson** *et al.*, **Kasperson** *et al.* and **Lemelson**, respectively. Claim 1 incorporates claim 5 to recite that a construct comprising an alpha emitting isotope conjugated to an antibody via a bifunctional chelant has a specific activity designed to deliver a minimum of one alpha track to a tumor upon systemic administration of an appropriate dose of the construct as further discussed *infra*. Administration of one dose will reduce the size of the tumor. Repeated administrations further reduce the tumor size to kill the tumor. Also, claim 1 is amended to recite that the tumor is in a human.

The amendment to claim 4 recites the range of specific activities from which a value for the construct is selected to be about 0.1 mCi/mg to about 30 mCi/mg. Claim 7 is amended to narrow the dose to about 0.1 mg/m^2 to about 25 mg/m^2. No new matter is added in these claim amendments.

The 35 U.S.C. §112, first paragraph rejections

Claims 1, 3-5 and 7 stand rejected under 35 U.S.C. 112, first paragraph as containing new matter. Applicants respectfully traverse this rejection.

The Examiner states that the specification does not teach a method of killing a tumor greater than 1 mm in size by administering an alpha emitting isotope and an antibody or antibody fragment specific for the tumor "at least once". Furthermore, the specification does not teach that the number of administrations of the claimed construct necessary to kill the tumor increases as the size of the tumor increases.

Applicants have amended the claims to remove this language. Amended claim 1 now recites systemically administering a dose of the alpha emitting isotope/antibody construct specific for the tumor where a high specific activity value is selected from a range such that the construct binds sufficient sites on a tumor cell to deliver at least one alpha particle to the tumor cell thereby reducing the size of the tumor. A subsequent step repeats administration to a human where each repeated administration reduces the tumor size

thereby killing the tumor. The specification teaches the necessity of determining a high specific activity to insure delivery of at least one alpha particle to a tumor cell to kill it; small quantities of Bi-213 on labeled ligands will not kill solid tumors (pg. 13, ll. 16 to pg. 17, ll. 17). Additionally, the specification teaches that one administration of a high specific activity B-213 construct reduces the size of a tumor which subsequently did not grow, in comparison to a control, and that repeated administration would kill the remaining tumor (pg. 11, ll. 3-10 pg. 39, ll. 5-17; Fig. 2).

Claims 1, 3-5 and 7 are rejected under 35 U.S.C. 112, first paragraph as lacking enablement for a method of killing a solid tumor using a construct comprising an antibody or an antibody fragment specific to the tumor and an alpha emitting isotope for reasons of record in paper no. 6. Applicants respectfully traverse this rejection.

The Examiner states that a construct comprising an antibody and an alpha emitting isotope encompasses a composition comprising an antibody and an alpha emitting isotope that are put together and not necessarily conjugated. Thus it is unpredictable

that using the claimed construct, the alpha emitting isotope would be targeted to the tumor and that the claimed method would be effective in killing solid tumors. Further, as stated in paper no. 6, the Examiner maintains that **Adams** *et al.* (Nuclear Med Biol, Vol. 27, pp. 3339-346 (2000) teach that single chain Fv and diabody are not effective in selectively killing tumors when coupled with Bi-213.

Applicants have deleted antibody fragments from amended claim 1. Further, as discussed, the claims are amended to recite that the construct comprises an alpha emitting isotope conjugated to an antibody via a bifunctional chelant. The antibody targets specific binding sites on the tumor cell (pg. 32, ll. 7 to pg. 33, ll. 5). A bifunctional chelant is defined in the art as a chelator that specifically functions in this manner, i.e., it attaches a chelated metal as a conjugate to the antibody. Furthermore, a bifunctional chelant will chelate the isotope and couple it to the antibody such that the antibody can effectively target and bind to the binding site on the tumor cell while retaining the isotope within the chelant. The selection of an appropriate bifunctional chelant, radiometal and antibody is well within the abilities of one of ordinary skill in the art.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph as lacking enablement in administering the isotope/antibody or antibody fragment in a dose of about 0.1 mg/m^2 to about 50 mg/m^2 for reasons of record in paper no. 6. Applicants respectfully traverse this rejection.

The Examiner maintains that a dose of 50 mg/m^2 even at a low specific activity of 2 mCi/mg would seem to be to one of ordinary skill in the art to be lethal and non-practical. **Adams** *et al.* teaches that in a mouse a dose of 600 μCi is lethal (of record, p. 341, first col.). Thus, the Examiner states that a low specific activity of 2 mCi/mg would provide 1000 μCi using a 50 mg/m^2 dose assuming as in paper no. 6 that a mouse is approximately 10 cm in length.

Applicants have amended claim 7 to recite a dose of about 0.1 mg/m^2 to about 25 mg/m^2. Claim 1 has been amended to recite a solid tumor in a human and claim 4 has been amended to limit the range of specific activities to about 0.1 mCi/mg to about 30 mCi/mg. The specification teaches that a total dose of at least 2.8 mCi/kg in 4 partial doses may be administered on one treatment day

with escalations of 0.14 mCi/partial dose as needed. (pg. 57, ll. 19 to pg. 58, ll. 3). Thus, for a 6 ft. (195 cm) tall 180 lb (82 kg) man, this is 229 mCi. Such a dose level was administered without acute toxicity or extramedullary toxicity (p. 59, ll. 11-13). Applicants submit that 128 mCi in divided doses 20-30 mCi of Bi-213 have been administered currently without lethality or even dose limiting toxicity. In combination with cytarabine at full strength, similar doses are achieved without unexpected toxicities with complete remissions in some patients (**Burke** *et al.* Proc Am Soc Hema (2002)).

Applicants reiterate that a salient aspect of the instant invention, as recited in amended claim 1, is selecting an antibody with a specific activity high enough to deliver an alpha tract per tumor cell and administering the antibody construct at a sufficient dose to achieve this. Thus, as discussed, one must consider, inter alia, the size of the tumor, the number of binding sites and affinity of the antibody for the tumor. For example, for 10 times the number of sites, i.e., 200, 000 instead of 20,000 as disclosed in the instant Example, 10 times more antibody could be used, 100 mg vs. 10 mg,

and, consequently, 10 times less specific activity, and still achieve the same number of alpha hits per cell.

Claim 7 and claim 4 are dependent claims that limit the dose and specific activities to a range. It is well within the art for one of ordinary skill to determine dose and specific activity even without the further limitations recited in these dependent claims. Furthermore, as explained *supra*, a high dose to accommodate a higher number of binding sites requires a lesser specific activity comparatively with fewer binding sites. When considering the ranges in claims 7 and 4, the instant invention and **Burke** *et al.* both contemplate dose escalation and as the amounts of mCi so far successfully administered are without toxicity, one of ordinary skill in the art would reasonably be expected to select appropriate doses and specific activities for the tumor treated.

Claims 1, 3-5 and 7 are rejected under 35 U.S.C. 112, first paragraph as lacking enablement for a method of killing a solid tumor of any size for reasons of record in paper no. 6. Applicants respectfully traverse this rejection.

The Examiner states that it would be unpredictable that repeated killing of layers of tumor cells each time, within the limit of toxicity of Bi-212 and Bi-213, would be adequate to reduce the size of large tumors, e.g., tumors of 936 mm^3 as taught by **Hartman** *et al.* Due to severe toxicity including death by these radioisotopes, it is not clear how many times one could administer the claimed labeled antibody in a week. **Hartman** *et al.* teach that a large size tumor could at least double in size every 8 days or faster, for example 50% more in 2 days, with one treatment of Bi-212 labeled antibody (Fig. 6, pg. 4367) and that a 936 mm^3 tumor showed no reduction in size with one with one injection (pg. 4367, first col., end of first paragraph). Thus, in a large tumor the number of tumor cells not killed would be overwhelmingly much larger than the layers killed and since the remaining tumor cells would continue to multiply, one could not predict that the size of the tumor would be reduced.

The Examiner states that the 936 mm^3 tumor disclosed in **Hartman** *et al.* is 72 times bigger than Applicants' 5 mm tumor. Respectfully, reiterating Applicants' arguments of paper no. 9, the volume of a 5 mm tumor using, as is standard in the art and used by

Hartman *et al.*, V = L x (W x W)(3.14)/6 is 62. 5 mm^3 and so a tumor volume of 936 mm^3 is approximately 15 times the volume. However, what is significant are the length and width of the tumor. This tumor has dimensions of 14.4 mm x 11.4 mm that are only about 2.3-2.9 times the size of Applicants' tumor.

Hartman *et al.* use a Bi-212 labeled anti-Tac antibody with a specific activity of 5.9-9.3 μCi/μg which is equivalent to 5.9-9.3 mCi/mg (pg. 4364, first col., second paragraph). The SP2/Tac cell line expresses 18,000 binding sites on its cell surface (pg. 4363, first col., end of first full paragraph). The instant application teaches that for a cell line expressing about 10,000–20,000 binding sites, e.g., HL60, a minimum specific activity of 10 mCi/mg is needed to deliver 2 Bi-213 or Bi-212 atoms per cell so that at least one alpha particle is tracked through the cell (pg. 16, ll. 1-13; pg. 36, ll. 3-4).

Hartman *et al.* did not appear to radiolabel the anti-Tac antibody to yield a particular specific activity as evidenced by the range of specific activities generated and the recitation of only the total μCi administered. Assuming, *arguendo*, that the anti-Tac

antibody is similar to the CD 33+ antibody used in the example in the instant application, i.e., with regard to antigen type, IL-2Rα (CD 25) and CD 33+ HL60, number of binding sites, 18,000 and 10-20,000, affinity 5nM and 1nM, radioisotope, Bi-212 and Bi-213, respectively, then even a construct with a specific activity of 9.3 mCi/mg possibly would be equivalent to the minimum of 10 mCi/mg required. **Hartman** *et al.* state that a single administration of 200 μCi did not reduce the size of large established tumors (pg. 4367, first col., end of first paragraph).

Hartman *et al.* did not repeat the administration of the 200 μCi nor is a suggestion found that a higher specific activity may be more effective. Applicants submit that the data in **Hartman** *et al.* serve to reinforce the necessity of selecting an appropriately high specific activity for the labeled antibody. This is particularly valid when considering that the anti-Tac antibody had an affinity for IL-2Rα antigen 5 times that of the antibody used in the instant example assuming a similarity of other features. As such, the statement in **Hartman** *et al.* that 200 μCi of Bi-212 anti-Tac did not reduce the size of large established tumors is misleading.

With regard to a large established tumor 14.4 mm x 11.4 mm in size certainly a single dose of Bi-212 or Bi-213 will not kill the tumor, however, it did significantly reduce the rate of growth in comparison to untreated control. In measuring % increase in relative tumor volume, **Hartman** *et al.* established that the untreated control increased in volume by 50% in ~2 days and doubled in volume in ~4 days in comparison to the ~8 days required after treating with a Bi-212-anti-Tac with an insufficient or minimal specific activity. The increase in tumor size of the treated tumor at day 2-3 is negligible, particularly considering tumor dimensions corresponding to the tumor volume.

One of ordinary skill in the art would also consider that human tumors do not double in size in 8 days; the rates of human cell lines in mice are not relevant to what works in people. The doubling time of most human solid tumors is measured in weeks with possibly the exception of high grade lymphomas and leukemias. The instant application states that most tumor cells have a doubling time of 2-15 days, however, this is amount of cells and not doubling time for the size of a tumor.

In a large solid tumor it is known that tumor cells farther than about 200 μm from a source of oxygen or food, i.e., from the vasculature, are not growing or viable. Thus, alpha emittors can be used to kill large tumors because the viable cells will always be within a short range of blood vessels and the alpha emitting constructs systemically administered thereto. Because not all of the tumor is growing or viable, repeated administrations of the construct will continuously kill more viable cells faster than the tumor can grow. Therefore, Applicants submit that repeated doses of 200 μCi of Bi-212 anti-Tac every 2-3 days at the least would have prevented the tumor from increasing in size even in a faster growing tumor in a murine model.

If in the original 14.4 x 11.4 tumor disclosed in **Hartman** *et al.*, a dose of antibody having a specific activity high enough to reduce the tumor size is administered every 2-3 days for a few weeks, which is the protocol described in the instant specification and cited *supra*, then the tumor would be unable to grow prior to the next dose and would eventually be eliminated. Thus, with such a protocol and the appropriately selected high specific antibody

construct and dose administered it is reasonable to assume that a large solid tumor can be killed. It is well within the purview of one of ordinary skill in the art to monitor the progress of the radiotherapy and to assess if and when additional radiotherapy is required.

Particularly, Applicants reiterate that the instant application teaches that one administration of a high specific antibody construct reduced the tumor size sufficiently that no further increase in size was apparent when compared to the control which doubled in diameter during the same period of time (Fig. 2). Furthermore, treating a 5 mm macroscopic prostate tumor *in vivo* with one dose of Bi-213 labeled J591 antibody specific for prostate cancer cells demonstrated a significant decrease in the rate of increase of measurable serum PSA in comparison to control. Seven days after a single treatment mice given the control antibody showed a mean 26% rise in PSA whereas mice treated with the specific J591 antibody showed only a mean 6% rise (pg. 43, ll. 4-16).

Accordingly, in view of the claim amendments and arguments presented supra, Applicants respectfully request that the

rejection of claims 1, 3-5 and 7 under 35 U.S.C. 112, first paragraph, be withdrawn.

The 35 U.S.C. §103 (a) rejection

Claims 1, 3-5 and 7 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Simonson** *et al.* (Cancer Res., 50(3 Supp): 9855-9885 (1990)), in view of **Kasperson** *et al.* (*Nuclear Med Comm*, 16, pp. 468-476 (1995)) and **Lemelson** (U.S. Patent No. 4,665,897). Applicants respectfully traverse this rejection.

The Examiner states that **Simonson** *et al.* teach administration of 212-Bi labeled antibodies to mice previously injected with LS1744T cells which grow as solid tumors and ascites in mice; ascites develop in the mice at about 20 days (p. 985s, second col. last paragraph) and only after the development of solid tumor (p. 987s, second col. first paragraph). The specific activity of the labeled antibody is 5-10 μCi/μg (p. 986s, first col., second paragraph). Additionally, for advanced tumors of 13 days and average tumor mass of 3 grams after injection of tumor cells with single and repeated administration of Bi-212 labeled antibody, 56% decreases in tumor mass is obtained (p.986s, first col., third paragraph; Fig. 1).

With regard to **Kaspersen** *et al.* the Examiner states that the reference teaches that Bi-213 can be an alternative to Bi-212 with the advantage of safer and easier production (p. 475, first col., first paragraph). Additionally, the Examiner states that **Lemelson** teaches a method of treating tumors by administering antibodies containing inactive nuclide that can be rendered radioactive with externally generated radiation. These steps can be repeated as many times as necessary to effect remission or destruction of tumors (Claims 28 and 35-36). The radiation may be alpha particles (Claim 27).

Thus it would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to treat tumors of at least 1 mm in size using the method of **Simonson** *et al.* in administering an antibody labeled with Bi-212. The Examiner submits that the tumors in **Simonson** *et al.* are at least 1 mm in size as they have a mass of 3 gm after 13 days of growth. It would have been obvious to use Bi-213 for the reasons taught by **Kaspersen** *et al.* It would have been obvious to administer the labeled antibody at least once or repeatedly as taught by **Simonson** *et al.* and

Lemelson. As to dosage recited in claims 5 and 7, to determine dosage is within the level of ordinary skill in the art. Thus, one of ordinary skill in the art would have been motivated to treat tumors having at least 1 mm in size using antibodies labeled with Bi-213 with a reasonable expectation of success.

Simonson *et al.* teaches that Bi-212 may be appropriate for the treatment of peritoneal implant metastases and ascitic cancer when administered intraperitoneally. The use of a Bi-212 labeled B72.3 antibody against the human colon carcinoma cell line LS174T in a murine model is examined (pg. 985s, first col., last paragraph to second col., second paragraph). The specific activity of the labeled antibody was 5-10 μCi/μg. **Simonson** *et al.* demonstrate that a single i.p. injection of 450 μCi or 3 consecutive i.p. injections of 190 μCi 13 days after tumor inoculation reduced tumor mass by 56%. These tumors were considered to be well advanced (pg. 986s, first col., third paragraph). In a model using smaller tumors four consecutive i.p. doses starting at day 8 of either 90 μCi or 180 μCi reduced tumor mass on average 85% with all mice in any regimen demonstrating some toxicity (pg. 986s, first col., fifth paragraph).

Simonson *et al.* state that despite a prolonged survival in some of the mice and significant reduction in tumor burden, a cure in none of them was obtained even with administration of 4 x 180 μCi on consecutive days to a tumor 8 days after inoculation (pg. 987s, second col., first paragraph). Furthermore, **Simsonson** *et al.* consider administration of a large single dose to be equivalent to consecutive multiple doses to reduce tumor burden. Multiple dosing was implemented because it was more convenient to elute the bismuth-212 generator (pg. 986s, first col., fourth paragraph). Thus, one of ordinary skill in the art could consider **Simonson** *et al.* to have administered one dose in four partial doses.

Kasperson *et al.* examined the cytotoxicity of Bi^{-213} *in vitro* and Ac^{-225} immunoconjugates against the human carcinoma cell lines A431 and SW1398. The reference discloses that Bi^{-213} may be substituted for Bi^{-212} for the treatment of single cell malignancies (pg. 475, col. 1, line 3). In an in vivo spheroid model no specific cell-killing was observed using up to 1.2 μCi Bi^{-213} on spheroids with diameters of 0.4 mm to 0.7 mm. **Kasperson** *et al.* state that Bi^{-213}

may have limited applicability in the treatment of solid tumors (pg. 474, last paragraph).

Lemelson teaches methods of detecting, monitoring and treating a tumor by administering a drug unit comprising a monoclonal antibody and a normally nonradioactive or inactive nuclide. The inactive nuclide such as boron-10 is activated by external radiation such as neutron radiation which in high levels can cause the inactive nuclide to emit a radioactive particle, e.g., alpha, beta or gamma. The inactive nuclide/antibody is administered again, activated and the monitoring process repeated until treatment ceases (Abstract; col. 12, lines 1-69; col. 13, lines 1-28).

Applicants' invention is as discussed *supra*. As amended, what is significant is that based on the selection of alpha emittor and antibody for the tumor type, a value for a high specific activity is selected from a range of values. Thus, a construct comprising the alpha emittor/antibody having this high specific activity can be administered to a human having a solid tumor of at least 1 mm in size in a dose that delivers at a minimum one alpha track per cell which reduces the size of the tumor. Each repetition of this dose

further reduces the tumor size to kill the tumor. The alpha emittor may be any alpha emittor; an appropriate specific activity can be determined from the range disclosed given a specific antibody.

When determining a prima facie case of obviousness, what must be considered is what is fairly taught by the prior art. One can not pick and choose elements without giving due consideration to how these elements function within the context of the invention. Additionally, there must be a motivation to combine the elements of the prior art with a reasonable expectation of success.

Simonson *et al.* do not teach or suggest administering further doses to effect a cure in their murine model. In fact, they state the efficacy of the Bi-212 labeled B72.3 antibody was reduced because (1) the antigen was secreted and not a cell surface antigen; (2) at 7-13 days the solid tumor was large and well-established; and (3) ascites did not form until well after establishment of the solid tumor. **Simonson** *et al.* hypothesize that Bi-212 may be effective against peritoneal/ascitic cancers if ascites form sooner while any solid tumor is smaller (pg. 987s, second col., first paragraph). Thus, at

most there is a suggestion to try a Bi-212 labeled antibody targeted to a cell surface antigen on a smaller peritoneal tumor which teaches away from the instant invention.

One must also consider that **Simonson** *et al.* correlate size with weight. Even though **Simonson** *et al.* consider a tumor 7-13 days after innoculation to be large and well established and that the Examiner states that the tumors in **Simonson** *et al.* are at least 1 mm in size as they have a mass of 3 gm after 13 days of growth, these tumors are peritoneal tumors and line the intraperitoneal cavity. **Simonson** *et al.* state that at the time of dissection of the mice, the LS174T tumor had spread over the internal organs and along the lining of the peritoneum (pg. 985s, second col., last paragraph). Therefore, what **Simonson** *et al.* consider to be a large solid tumor weighing 3 gm could actually be a paper thin tumor covering a large intraperitoneal area. As such, **Simonson** *et al.* could still not effect a cure.

Kaspersen *et al.* teaches the use of Bi-213 as a replacement for Bi-212 in the treatment of single cell malignancies but further states that Bi-213 may have limited applicability in the

treatment of solid tumors. This statement is reinforced when considering, that despite safer and easier production of Bi-213, Bi-21 has a half-life about 33% longer than that of Bi-212. When specific activity is not taken into consideration and administration is contemplated to be only once, it is therefore not as effective as Bi-212 under these conditions.

Lemelson teaches an inactive nuclide/antibody may be administered to target a tumor and subsequently caused to emit an alpha particle via neutron bombardment of the inactive nuclide with such treatment being repeated as needed. At best this teaches that alpha particles can be repeatedly used at the site of a targeted tumor to destroy the tumor. This is neither a teaching nor a suggestion that an alpha-emitting radioactive isotope/antibody can be directly administered in that form to effect treatment. Such teaching would preclude the step of neutron bombardment or other application of external radiation and is contrary to the claimed method recited in **Lemelson**. Applicants also submit that Lemelson only actually teaches how to make the compositions disclosed therein and no actual teaching is found that practically the method is effective in a

human. In fact, Applicants submit that to date boron neutron capture has not successfully been used systemically because it is not possible to generate enough boron at a site locally by systemic administration to allow enough capture.

As demonstrated with **Hartman** *et al.*, the specific activity of the Bi-212 construct in **Simonson** *et al.* varied between 5-10 μCi and may be insufficient to form a minimally high specific activity construct. Although **Simonson** *et al.* suggest that Bi-212 would have been more effective if a monoclonal antibody that targets a cell surface antigen was used, no suggestion is found that the inability to cure the tumors is due, *inter alia*, to an insufficient specific activity for the Bi-212/antibody construct used. Additionally, **Simonson** *et al.* not only administered the Bi-212 construct intraperitoneally, but the antibody targeted a secreted antigen. As stated *supra*, the instant invention works because the alpha-emitting construct is administered systemically, targets the cell surface directly and can deliver at least one alpha tract to a cell.

Thus, absent a suggestion or teaching in **Simonson** *et al.* to select a higher specific activity Bi-212 construct with systemic

administraton to assure delivery of a minimum of one track per cell in a tumor upon repeated targeting by the antibody, the suggestion by **Kaspersen** *et al.* to replace Bi-212 with Bi-213 is moot. This is particularly in view of the statement that Bi-213 may have limited applicability for solid tumors which is supported by the suggestion in **Simonson** *et al.* that peritoneal tumors would be better treated if ascites formed when the tumor was smaller and less established in the peritoneal cavity. Additionally, even if one of ordinary skill in the art should be motivated by **Lemelson** to repeat administrations of the radiolabeled antibody, this is still not Applicants' invention.

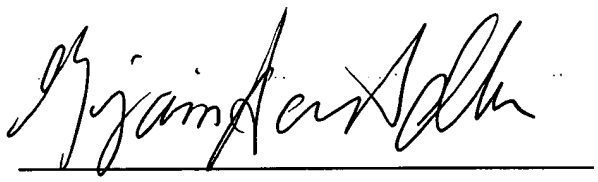
Finally, claim 5 is canceled and claims 3-4 and 7 depend from amended claim 1 and further limit the alpha emitting isotopes, the range of specific activities and the range of doses. If **Simonson** *et al.* in combination with **Kaspersen** *et al.* and **Lemelson** do not render amended claim 1 obvious, then neither are claims depending from claim 1 obvious in view of the combination. Thus, the invention as a whole was not prima facie obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, in view of the claim amendments and arguments presented supra, Applicants

respectfully request that the rejection of claims 1, 3-5 and 7 under 35 U.S.C. 103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed November 20, 2002. If any issues remain, the Examiner is respectfully requested to telephone the undersigned attorney for immediate resolution. Applicants believe that no fees are due, however, should this be in error, please debit Deposit Account No. 07-1185 on which the undersigned is allowed to draw.

Respectfully submitted,

Date: Feb 21, 2003



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VERSION WITH MARKINGS TO SHOW CHANGES MADE IN THE CLAIMS:

Please amend claim 1 as follows:

1. (twice-amended) A method of killing a solid tumor greater than 1 mm in size in ~~a n~~ a human ~~individual~~ in need of such treatment, comprising the steps of:

(a) selecting an antibody that targets a specific binding sites on a tumor cell;

(b) selecting an alpha particle-emitting isotope;

(c) selecting a value for a high specific activity for an alpha particle-emitting isotope/antibody construct from a range of specific activities, said construct comprising said isotope conjugated to said antibody via a bifunctional chelant;

wherein said range of specific activities is such that the value selected is at least sufficient for a pharmacologically effective amount of a dose of said construct to provide an amount of antibody to bind to a plurality of targeted sites on the tumor cell wherein at least one alpha track per tumor cell is delivered thereto from said isotope upon binding of the antibody;

Check wording?

(d) systemically administering ~~a pharmacologically effective~~ the dose of ~~a~~ said high specific activity construct ~~at least once~~ to said ~~individual~~ human, whereupon the size of the tumor is reduced, ~~said construct comprising an antibody or an antibody fragment specific to said tumor~~; and; and

~~an alpha emitting isotope; wherein the number of administrations of said construct necessary to kill said tumor increases as the size of said tumor increases;~~

(e) repeating step (d) wherein each repetition further reduces the size of the tumor thereby killing the tumor.

Please amend claim 4 as follows:

4. (twice-amended) The method of claim 1 ~~3~~, wherein said range ~~alpha emitting isotope has a~~ of high specific activity is ~~of from~~ about 0.1 mCi/mg to about 30 ~~50~~ mCi/mg.

less than 10 mCi/mg

Please amend claim 7 as follows:

7. (twice-amended) The method of claim 1, wherein said dose is from about 0.1 mg/m^2 to about 25 ~~50~~ mg/m^2.

Please cancel claim 5.